Published in final edited form as:

Ophthalmology. 2011 May ; 118(5): 895–901. doi:10.1016/j.ophtha.2010.09.017.

Visual field loss among patients with cytomegalovirus retinitis

Jennifer E. Thorne, MD, PhD^{1,2}, Mark L. Van Natta, MS², Douglas A. Jabs, MD, MBA^{2,3},
Jacque L. Duncan, MD⁴, Sunil K. Srivastava, MD⁵, and Studies of Ocular Complications of
AIDS (SOCA) Research Group⁶

¹Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland ²Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland ³Departments of Ophthalmology and Medicine, Mount Sinai School of Medicine, New York, New York ⁴Department of Ophthalmology, University of California, San Francisco, San Francisco, California ⁵Department of Ophthalmology, Emory University, Atlanta, Georgia ⁶Members of the SOCA Research Group are listed online

Abstract

Purpose—To describe visual field (VF) loss among patients with cytomegalovirus (CMV) retinitis and the risk factors for such loss.

Design—Multicenter, prospective, observational study

Participants—476 patients with AIDS and CMV retinitis and VF data

Methods—Follow-up every 3 months with medical history, ophthalmological examination, Goldman visual fields, and laboratory testing

Main outcome measures—Incidence of visual field loss in eyes affected with CMV retinitis and characteristics associated with such VF loss

Results—Over a median follow up of 4 years (range = 0.5 to 9 years), the incidence rates of VF loss to 75% and 50% of normal were 0.22/eye-year (EY, 95% confidence interval [CI]: 0.20, 0.25) and 0.08/EY (95% CI: 0.06, 0.10), respectively. The observed rates were 6- to 7-fold less than those observed rates of VF loss in the era prior to highly active antiretroviral therapy (HAART). Decreased CD4+ T cell count, whether measured at enrollment or over follow up time, was associated with increased rates of VF loss for all VF outcomes in a dose-dependent fashion. Risk factors for VF loss included lower CD4+ T cell count, CMV lesion size >25% of the total retinal area, and active CMV retinitis after controlling for potential confounding. HAART use and immune recovery (CD4+ T cell count >100 cells/μL) were associated with reduced risk of VF loss in multiple regression models. Immune recovery was statistically significantly associated with a lower risk of VF loss to 75% of normal (relative risk [RR] = 0.63 95% CI: 0.49, 0.86 P = 0.003) and to 50% of normal (RR = 0.60 95% CI: 0.44, 0.82 P = 0.001) after controlling for demographic

© 2010 American Academy of Ophthalmology, Inc. Published by Elsevier Inc. All rights reserved.

Corresponding Author: Jennifer E. Thorne, MD, PhD, 550 North Broadway, Suite 700, Baltimore, MD 21205; phone 410-955-1966; fax: 410-955-0629; jthorne@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosures: Dr. Jabs is a paid consultant or serves on the advisory boards of the following: Allergan, Genzyme, Abbott Laboratories, Novartis Pharmaceuticals Corporation, Roche Pharmaceuticals, and GlaxoSmithKline. Dr. Srivastava is a paid consultant for Bausch and Lomb, Allergan Inc., and Novartis Pharmaceuticals Corporation.

characteristics, human immunodeficiency virus (HIV) viral load, HAART use, CMV lesion location and size, and retinitis activity.

Conclusions—Cytomegalovirus retinitis was associated with a substantial risk of incident VF loss, but the incidence is approximately 6- fold lower than that observed in the pre-HAART era. Those who have HAART-induced immune recovery have approximately 40% lower risk of visual field loss for both outcomes after controlling for confounding.

INTRODUCTION

Cytomegalovirus (CMV) retinitis is a common opportunistic disease among patients with the acquired immunodeficiency syndrome (AIDS).¹⁻³ Before the introduction of highly active antiretroviral therapy (HAART), 30% of patients developed CMV retinitis during their lifetime,⁴ and CMV retinitis resulted in substantial loss of visual acuity^{1,5} and of visual field.⁶ Treatment with HAART suppresses human immunodeficiency virus (HIV) replication in the blood, which may allow for immune recovery and restored anti-CMV immunity.^{7,8} Immune recovery has resulted in a declining number of opportunistic infections, including an approximate 80% reduction in the incidence of CMV retinitis.^{7,9,10} Patients with CMV retinitis who have immune recovery are less likely to have progression of retinitis,¹¹ to develop retinal detachment complicating CMV retinitis,^{12,13} and to have loss of visual acuity than are patients without immune recovery.^{14,15} The effects of immune recovery on the rates on visual field (VF) loss are not known. It is likely that patients with immune recovery will have decreased rates of VF loss. Furthermore, it also is possible that patients taking HAART will have lower rates of VF loss even without immune recovery as patients on HAART with insufficient immune recovery have some improvement in their CMV retinitis outcomes (e.g., progression of CMV retinitis¹¹ and visual acuity¹⁵). To address these questions, we analyzed data from a prospective observational study of 476 patients with AIDS and CMV retinitis.

Methods

Study population

The Longitudinal Studies of the Ocular Complications of AIDS (LSOCA) is a prospective multicenter observational study of patients with AIDS.¹⁶ Patients with the diagnosis of AIDS aged 13 years or older are eligible. AIDS is diagnosed according to the 1993 Centers for Disease Control and Prevention Revised Surveillance Case Definition.¹⁷ Patients were enrolled with or without CMV retinitis however, this report focuses on patients with CMV retinitis in the study. This study was approved by the Institutional Review Board at each participating center and the three resource centers. The study was conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent prior to participating in the study.¹⁶

Data collection

Data collection at enrollment and follow-up visits included medical and ophthalmologic histories, complete ophthalmic examination, CD4+ T cell counts, and plasma HIV viral load assessment and have been described previously.^{12,15,16} Cytomegalovirus retinitis was diagnosed by ophthalmic examination by a study-certified ophthalmologist based on its characteristic appearance.¹⁸ Zone 1 is defined as the area within 1500 μ m of the optic nerve or within 3000 μ m of the center of the macula. Zone 2 extends from Zone 1 to the vortex veins and Zone 3 lies anterior to the vortex veins.¹⁹ Patients were seen every 3 months for the follow up period. Immune recovery was defined as a CD4+ T cell count > 100 cells/ μ L for the purposes of this study. Visual fields were evaluated for each eye of each patient every three months using Goldman perimetry. A modified diabetic retinopathy study (DRS)

visual field score was determined for Goldman field results.²⁰ The Goldman visual field (GVF) score was derived for each eye by calculating the sum of the degrees seen along each 30-degree meridian using the I-4 and the IV-4 test object.^{20,21} This method, used previously in the unaffected eyes of patients with AIDS and CMV retinitis,²⁰ derived a normal GVF score of 700 ± 100 degree, which was used in Studies of Ocular Complications of AIDS (SOCA) studies prior to the advent of HAART. These findings were further validated in a study of 20 healthy, HIV negative, adult patients without any eye disease.²¹ Among these patients, the GVF values were higher (normal mean GVF score = 800 degrees standard deviation = 50 degrees), and these data were used to modify the cutoff thresholds for the analyses involving the patients with CMV retinitis in LSOCA described herein. The threshold for abnormal visual field score was defined as worse than 2 standard deviations from the mean normal visual field score (e.g., < 700 degrees).²¹

Main outcome measures

Primary outcomes measures were loss of VF to 75% (VF score of 600 or less) and 50% (VF score of 400 or less) of normal as calculated above. Secondary outcomes were a score of 700 or less (2 standard deviations from mean normal VF score) and 90% loss (VF score of 80 or less) which corresponds to the visual field definition of blindness.

Statistical analysis

Data collected and reported to the SOCA Coordinating Center as of 31 July 2008 were included in this report. All patients with CMV retinitis and with follow up data as of that date were included in these analyses. Rates were defined as the number of events divided by the total eye-years at risk for the event for all eyes affected with CMV retinitis. For the better-seeing eye analyses, rates were calculated as the number of events in the eye with the better (e.g., higher) VF score of each patient divided by the total person-years at risk. Time to event graphs were generated using the Kaplan Meier method.²² Relative risks were estimated using Cox regression.²³ P values were nominal and 2-sided. Multiple regression models containing all exposure variables with statistically significant associations for each VF outcome, and models generated by stepwise procedures with the cutoff for inclusion in the final model of $P < 0.05$ were constructed. All multiple regression models controlled for demographic characteristics including age, gender, race, and HIV risk factor. Correlations between exposure variables selected for the multiple regression analyses were checked. When two variables were highly correlated (for these analyses CD4+ T cell count and presence of immune recovery were the only variables that were highly correlated), separate regression models were constructed using one of the two variables and the best-fitting model was selected. Univariate analyses did not include patients with missing values. For multiple regression analyses, observations with missing values were imputed with the value from the most frequent category. All analyses accounted for correlation between eyes in patients with bilateral disease using robust techniques.²⁴ Analyses were performed with the Stata 9.0 statistical package (Stata Corporation, College Station, TX).

Results

Characteristics of the study population

Characteristics at enrollment of the 476 patients with CMV retinitis in at least one eye are summarized as Table 1 (available at <http://aaojournal.org>). The median age of these patients was 41 years (interquartile range: 35-46 years). Approximately 80% were men 47% patients were white, 31% were black, non-Hispanic, and 18% were Hispanic. The HIV risk factor of men who had sex with men was reported in 59% of patients, heterosexual contact was reported in 25% of patients, and injection drug use was reported in 7% of patients. The median nadir CD4+ T cell count was 10 cells/ μ L. Approximately 79% of patients were

receiving HAART at the time of enrollment 64.2% receiving a protease inhibitor as part of the HAART regimen and 14.7% receiving a HAART regimen that did not include a protease inhibitor. The majority of patients had received HAART at some time prior to enrolling in LSOCA (81.6%), with a median duration of HAAART treatment of 2.2 years. Half of patients had immune recovery at the time of enrollment.

Thirty-nine percent of patients had bilateral CMV retinitis. Of the 662 eyes affected with CMV retinitis, 233 eyes (35.2%) had retinitis that involved 25% or greater of the total retinal area, and 241 eyes (36.4%) had retinitis that involved the optic nerve or macula region (Zone 1 disease). Approximately 10% of eyes had immune recovery uveitis (IRU) at baseline. At the time of enrollment, 37% of eyes with CMV retinitis had received ganciclovir implants and 30% of eyes received systemic ganciclovir. Approximately one-quarter of affected eyes were not receiving any anti-CMV therapy at the time of enrollment (27.1% of affected eyes) 17.3% were eyes of patients who had immune recovery. There were 64 eyes in 47 patients who were not receiving any anti-CMV therapy and did not have immune recovery at the time of enrollment. Of these 64 eyes, 28 received anti-CMV therapy within six month of enrollment (25 eyes with ganciclovir implant and 3 with intravitreal injections) 24 eyes had inactive CMV retinitis at enrollment and the patients developed immune recovery during follow up and did not receive additional anti-CMV therapy the remaining 12 eyes were in patients who either died or were lost to follow up prior to receiving anti-CMV therapy.

Among eyes affected with CMV retinitis, 190 eyes (29.4%) had a baseline visual acuity of 20/50 or worse and 95 eyes (14.5%) of eyes had a baseline visual acuity of 20/200 or worse. At the baseline examination, approximately one-half of affected eyes had loss of visual field to 75% of normal (visual field score < 600 in 56.2% of eyes) and one-quarter had loss to 50% of the normal visual field (visual field score < 400 in 25.8% of eyes).

Incidence of visual field loss in eyes with CMV retinitis

Over a median follow up period of 4 years (mean: 5 years range: 6 months to 9.2 years), the overall incidence rates of VF loss to 75% and 50% of normal were 0.22/eye-year (EY) and 0.08/EY, respectively among eyes with CMV retinitis. In the better-seeing eyes of all patients with CMV retinitis, the rates of VF loss to 75% and 50% of normal were 0.06/person-year (PY) and 0.01/PY. Incidence rates of VF loss according to CD4+ T cell count at the time of enrollment are summarized as Table 2 (available at <http://aaojournal.org>). Rates of VF loss were statistically significantly higher among patients with lower CD4+ T cell counts at enrollment for all four visual field outcomes (P value for trend < 0.001 for VF loss to < 700, and to 75% and 50% of normal. P value for trend = 0.02 for VF loss to 10% of normal).

Risk factors for incident visual field loss

The relationship of demographic and clinical characteristics to the incidence of VF loss in eyes with CMV retinitis is summarized in Tables 3 and 4. Demographic characteristics did not appear to be associated with an increased risk of VF loss. Lower CD4+ T cell count and detectable HIV viral load were associated with increased rates of VF loss for both outcomes. Similar results were seen whether the CD4+ T cell count and HIV viral load were evaluated as time-dependent variables (Table 3) or by using baseline values only.

Use of HAART was associated with reduced incidences of visual field loss to 75% and 50% of normal. Eyes of patients with immune recovery (defined as CD4+ T cell count > 100 cells/ μ L) had lower rates of VF loss to 75% of normal (Figure 1a) and to 50% of normal (Figure 1b) when compared to eyes of patients without immune recovery at baseline (0.17/

EY versus 0.41/EY, $P < 0.001$ 0.06/EY versus 0.14/EY, $P < 0.001$, respectively). The presence of immune recovery uveitis was not associated with an increased rate of VF loss for either outcome.

Rates of VF loss also were statistically different between eyes treated with the ganciclovir implant(s), with intravitreal injections, or with systemic anti-CMV therapy. The rates of VF loss among eyes receiving intravitreal injections for CMV retinitis were particularly high (Table 3). However, approximately 75% of the eyes receiving intravitreal ganciclovir injections had immediately vision-threatening retinitis (e.g., Zone 1 disease) and 54% of these eyes also had large lesion size ($>25\%$ of total retina involved with CMV retinitis). Of the 177 eyes that did not receive anti-CMV therapy, 64% were eyes of patients who had immune recovery. Eyes of patients with immune recovery who did not receive anti-CMV therapy had lower rates of VF loss to 75% and 50% of normal as compared to eyes of patients without immune recovery who did not receive anti-CMV therapy and comparable rates of VF loss to eyes that received ganciclovir implants (Table 3).

In the final multiple regression analysis (presented as Table 4), decreasing CD4+ T cell count, active CMV retinitis and larger CMV retinitis lesion size were associated with an increased risk of VF loss after adjusting for potential confounding by other characteristics including patient demographics, HIV viral load, use of HAART, and location (zone) of retinitis. Use of HAART was associated with a reduced risk of VF loss to 75% of normal after adjustment for confounding (relative risk [RR] = 0.72, 95% CI: 0.54, 0.95, $P = 0.02$). Immune recovery was not included in the final multiple regression analysis because it was highly correlated with the CD4+ T cell count ($r > 0.90$). However, when analyzed separately from CD4+ T cell count, immune recovery was associated with a reduced risk of VF loss to 75% and 50% of normal after controlling for confounding (RR = 0.63, 95% CI: 0.49, 0.86, $P = 0.003$ and RR = 0.60, 95% CI: 0.44, 0.82, $P = 0.001$, respectively). In this alternate model, use of HAART was associated with a reduced risk of VF loss to 75% of normal over and above the reduced risk associated with immune recovery (RR = 0.71, 95% CI: 0.54, 0.92, $P = 0.01$).

Discussion

The potential of HAART-related immune recovery has altered the course of CMV retinitis. 7-11-15 The rates for VF loss among eyes with CMV retinitis we observed in our cohort are approximately 6- to 7-fold less than the rates observed in pre-HAART studies.6 The incidence rates of VF loss to 50% and 90% loss of the total visual field in SOCA studies completed prior to HAART6 and in this study are summarized as Table 5. The reductions in VF loss we observed likely are due in part to reductions in the rates of CMV retinitis progression (and thus lesion size) and retinitis-related retinal detachment, which have been reduced by 96% and 88%, respectively in the HAART era and likely have contributed to the reductions in the rates of visual acuity loss as well.11-15 Despite this, VF loss among eyes with active CMV retinitis remains substantial, particularly for the 50% loss outcome, among patients not receiving HAART and those receiving HAART but without immune recovery (Table 5). Even among eyes of patients with immune recovery and without IRU (i.e., the patients who had the lowest rates of VF loss in our study), the rates are not zero and remain higher than the rates of vision loss among eyes of patients without CMV retinitis. Indeed, among patients with CD4+ T cell counts ≥ 200 cells/ μ L, the rates of VF loss were 0.18/EY and 0.06/EY for VF loss to 75% and 50% of normal field, respectively. Sensitivity analyses to ascertain the proximal cause of such VF loss were performed, and the overwhelming reason for VF loss among these patients was due to progression of retinitis. Further, the rates of VF loss to 75% and 50% of normal field among eyes of patients with AIDS but no CMV retinitis were 0.02/EY and 0.005/EY; therefore VF loss secondary to HIV neuroretinal

disease²⁵ did not contribute substantially to the loss of VF observed in the CMV retinitis cohort. Among eyes of patients with CMV retinitis who have immune recovery, the rate of progression of CMV retinitis is approximately 2% per eye per year.²⁶ These data support the recommendation for continued routine ophthalmologic follow up of patients with CMV retinitis every three months even if they have immune recovery and have successfully stopped anti-CMV therapy.^{7,11,15,26}

Improvement in CD4+ T cell count was associated with lower rates of VF loss. Eyes of patients achieving CD4+ T cell counts of >100 cells/ μ L (e.g., immune recovery) during follow up had a 37% lower risk of VF loss to 75% of normal and a 40% lower risk of VF loss to 50% of normal after controlling for confounding. Use of HAART was associated with a reduction in the risk of VF loss in our patients after controlling for immune recovery, but the association was statistically significant only for VF loss to 75% of normal. Previous studies also have suggested a beneficial effect of HAART on the incidence of moderate vision loss over and above the protective effect of immune recovery.^{14,15} It is conceivable that HAART may prevent visual loss through mechanisms other than immune recovery (i.e., reduced HIV load resulting in reduced transactivation of CMV²⁷), but such effects, if present, appear to be smaller than the effects mediated by improved immunity. The possibility of transient VF loss due to IRU or to cataract was considered. Including reversible VF loss in our analyses potentially could overestimate the rates of VF loss and bias our results. In order to account for reversible visual loss, sensitivity analyses evaluating only VF loss events that persisted for 2 or more consecutive visits (spanning approximately three months) were performed. In these analyses, the rates of VF loss were essentially unchanged (data not shown), suggesting that the majority of VF loss was due to CMV-related retinal necrosis. An analysis evaluating the proximate causes of VF loss among eyes with CMV retinitis demonstrated that 90.2% of the observed VF loss was attributable to necrosis of the retinitis, retinal detachment, and optic atrophy secondary to CMV retinitis.

We observed differences in the rates of VF loss among eyes treated with different types of anti-CMV therapies. Unlike previous reports of outcomes of anti-CMV therapy,¹¹⁻¹⁵ we observed that the ganciclovir implant was associated with lower rates of VF loss than those observed among patients treated with systemic ganciclovir in the univariate analyses. However, these differences did not achieve conventional statistical significance after controlling for HAART use and CD4+ T cell count. Further, the rates of VF loss among eyes treated with ganciclovir implants were similar to those observed in eyes of patients not receiving any anti-CMV therapy and who had undergone immune recovery. The large rates of VF loss among eyes receiving intravitreal injections for CMV retinitis are likely a result of treatment by indication bias as an intravitreal injection often is given for eyes with active retinitis that is immediately vision-threatening (e.g., in our study, 75% of eyes treated with intravitreal ganciclovir injections had Zone 1 retinitis at the time of treatment).

In summary, VF loss occurs among patients with CMV retinitis although rates of such loss are lower than those observed before the widespread availability of HAART. Improved immunity reduces, but does not eliminate, the risk of VF loss among these patients.

Acknowledgments

We thank Alka Ahuja, MS for statistical consultation.

Grant Support: Supported by agreements from the National Eye Institute, the National Institutes of Health, Bethesda, MD to the Mount Sinai School of Medicine, New York, NY (U10 EY08052) the Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD (U10 EY08057) and the University of Wisconsin, Madison, Madison, WI (U10 08067).

References

1. Jabs DA. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc.* 1995; 93:623–83. [PubMed: 8719695]
2. Jabs DA, Holbrook JT, Van Natta ML, et al. Studies of Ocular Complications of AIDS Research Group. Risk factors for mortality in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology.* 2005; 112:771–9. [PubMed: 15878056]
3. Pertel P, Hirschtick RE, Phair J, et al. Risk of developing cytomegalovirus retinitis in persons infected with the human immunodeficiency virus. *J Acquir Immune Defic Syndr.* 1992; 5:1069–74. [PubMed: 1357151]
4. Hoover DR, Peng Y, Saah A, et al. Occurrence of cytomegalovirus retinitis after human immunodeficiency virus immunosuppression. *Arch Ophthalmol.* 1996; 114:821–7. [PubMed: 8660165]
5. Studies of Ocular Complications of AIDS Research Group; AIDS Clinical Trials Group. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. 4. Visual outcomes. *Ophthalmology.* 1994; 101:1250–61. [PubMed: 8035989]
6. Holbrook JT, Jabs DA, Weinberg DV, et al. Studies of Ocular Complications of AIDS (SOCA) Research Group. Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before widespread availability of highly active antiretroviral therapy. *Arch Ophthalmol.* 2003; 121:99–107. [PubMed: 12523893]
7. Jabs DA. AIDS and ophthalmology, 2008. *Arch Ophthalmol.* 2008; 126:1143–6. [PubMed: 18695113]
8. Komanduri KV, Viswanathan MN, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med.* 1998; 4:953–6. [PubMed: 9701250]
9. Holtzer CD, Jacobson MA, Hadley WK, et al. Decline in the rate of specific opportunistic infections at San Francisco General Hospital, 1994-1997. *AIDS.* 1998; 12:1931–3. [PubMed: 9792398]
10. Jacobson MA, Stanley H, Holtzer C, et al. Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2000; 30:231–3. [PubMed: 10619774]
11. Jabs DA, Van Natta ML, Thorne JE, et al. Studies of Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. 1. Retinitis progression. *Ophthalmology.* 2004; 111:2224–31. [PubMed: 15582078]
12. Kempen JH, Jabs DA, Dunn JP, et al. Retinal detachment risk in cytomegalovirus retinitis related to the acquired immune deficiency syndrome. *Arch Ophthalmol.* 2001; 119:33–40. [PubMed: 11146724]
13. Jabs DA, Van Natta ML, Thorne JE, et al. Studies of Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology.* 2004; 111:2232–9. [PubMed: 15582079]
14. Kempen JH, Jabs DA, Wilson LA, et al. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. *Arch Ophthalmol.* 2003; 121:466–76. [PubMed: 12695243]
15. Thorne JE, Jabs DA, Kempen JH, et al. Studies of Ocular Complications of AIDS Research Group. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology.* 2006; 113:1432–40. [PubMed: 16766032]
16. Jabs DA, Van Natta ML, Kempen JH, et al. Studies of Ocular Complications of AIDS Research Group. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol.* 2002; 133:48–61. [PubMed: 11755839]
17. Castro HG, Ward JW, Slutsker L, et al. revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992. 1993; 41(RR-17):1–19.

18. Studies of Ocular Complications of AIDS (SOCA) Research Group; AIDS Clinical Trials Group (ACTG). Studies of Ocular Complications of AIDS Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 1. Rationale, design, and methods. *Control Clin Trials*. 1992; 13:22–39. [PubMed: 1315661]
19. Holland GN, Buhles WC Jr, Mastre B, Kaplan HJ, UCLA CMV Retinopathy Study Group. A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy: use of a standardized system for the assessment of disease outcome. *Arch Ophthalmol*. 1989; 107:1759–66. [PubMed: 2556989]
20. Studies of Ocular Complications of AIDS Research Group; AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the Cytomegalovirus Retreatment Trial. *Arch Ophthalmol*. 1996; 114:23–33. [PubMed: 8540847]
21. Thorne JE, Jabs DA, Kedhar SR, et al. Loss of visual field among patients with birdshot chorioretinopathy. *Am J Ophthalmol*. 2008; 145:23–8. [PubMed: 17997394]
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53:457–81.
23. Cox, DR.; Oakes, D. *Analysis of Survival Data*. Chapman and Hall; London: 1984. p. 248-75.
24. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc*. 1989; 84:1074–8.
25. Freeman WR, Van Natta ML, Jabs D, et al. SOCA Research Group. Vision function in HIV patients without retinitis: report of the Studies of Ocular Complications of AIDS Research Group. *Am J Ophthalmol*. 2008; 145:453–62. [PubMed: 18191094]
26. Jabs DA, Ahuja A, Van Natta M, et al. Studies of the Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology*. In press.
27. Jabs DA, Bartlett JG. AIDS and ophthalmology: a period of transition. *Am J Ophthalmol*. 1997; 124:227–33. [PubMed: 9262548]

Figure 1. Kaplan-Meier survival curves of time to loss to 75% (1a) and 50% (1b) of the normal visual field according to immune recovery status at enrollment in patients with AIDS and cytomegalovirus retinitis.

Table 1

Characteristics of patients with cytomegalovirus retinitis at enrollment

Patient-Specific Characteristics	N = 476
Demographics	% (n)
Median age, years (interquartile range)	41 (35-46) Range (17-68)
Race	
White, non-Hispanic	47.3 (225)
Black, non-Hispanic	30.7 (146)
Hispanic	17.7 (84)
Gender	
Men	80.2 (382)
Women	19.8 (94)
HIV risk factor	
Men having sex with men	59.4 (283)
Injection drug use	7.0 (33)
Heterosexual contact	25.3 (120)
AIDS/CMV history	
Duration of AIDS, years (interquartile range)	4.7 (2-7)
Anti-retroviral therapy at time of enrollment	
None	12.2 (58)
ART, no HAART	9.0 (43)
HAART	78.9 (375)
Duration of CMV retinitis, years (interquartile range)	1.7 (0.1-3.4)
Newly diagnosed CMV retinitis	24.8 (118)
Bilateral CMV retinitis	39.1 (186)
CMV viral load ≥ 400 copies/mL	11.1 (53)
Immunology & virology	
Nadir CD4+ T cell count in cells/ μ L, median (range)	10 (0-62)
CD4+ T cell count at enrollment	
< 50 cells/ μ L	37.2 (177)
50-100 cells/ μ L	12.8 (61)
101-199 cells/ μ L	15.7 (75)
≥ 200 cells/ μ L	34.3 (163)
HIV viral load ($\log_{10}$ [copies/mL])	
< 2.60 (undetectable)	38.9 (185)
Immune recovery*	50.0 (238)
Visual acuity, better-seeing eye	
Visual acuity 20/50 or worse	8.4 (40)
Visual acuity 20/200 or worse	1.9 (9)
Visual field, better-seeing eye	
Median visual field score (interquartile range)	640 (601-754)

Patient-Specific Characteristics	N = 476
Visual field score < 700 (2 standard deviations from the median)	46.9 (203)
Visual field score < 600 (= 75% of normal field)	21.0 (91)
Visual field score < 400 (= 50% of normal field)	6.7 (29)
Visual field score < 80 (= 10% of normal field)	0.7 (3)
Eye-specific Characteristics	N = 662
CMV retinitis	% (n)
Area of CMV retinitis ≥ 25% of retinal area	35.2 (233)
Zone 1 CMV retinitis	36.4 (241)
Optic nerve disease [†]	6.8 (45)
Cataract [‡]	15.1 (100)
Immune recovery uveitis	8.8 (58)
Anti-CMV retinitis therapy at time of enrollment ^{//}	
Ganciclovir implant	36.8 (240)
Systemic ganciclovir	29.9 (195)
Intravitreal injection	3.7 (24)
Other	2.4 (16)
No therapy without immune recovery [¶]	9.8 (64)
No therapy with immune recovery	17.3 (113)
Visual acuity, affected eyes	
Visual acuity 20/50 or worse	29.4 (190)
Visual acuity 20/200 or worse	14.5 (95)
Visual field, affected eyes	
Median visual field score (interquartile range)	583 (427-690)
Visual field score < 700 (= 2 standard deviations from the median)	79.3 (513)
Visual field score < 600 (= 75% of normal field)	56.2 (367)
Visual field score < 400 (= 50% of normal field)	25.8 (167)
Visual field score < 80 (= 10% of normal field)	7.4 (48)

AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; CMV = cytomegalovirus; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

* Immune recovery defined as a CD4+ T-cell count > 100/μL at enrollment.

[†] Optic nerve disease included: optic neuropathy associated with CMV retinitis; (21 eyes) optic atrophy (5 eyes); glaucoma (7 eyes); not specified (12 eyes).

[‡] Cataract defined as 1+ or greater opacities

^{//} Other CMV therapy included systemic foscarnet and cidofovir

[¶] Of the 64 eyes not receiving anti-CMV therapy at enrollment, 38 had inactive CMV retinitis and 26 had active CMV retinitis (17 eyes had ganciclovir implant surgery during follow up; 2 eyes also received intravitreal ganciclovir injections in addition to implants; 9 eyes did not receive any treatment).

Table 2

Rates of visual field loss among involved eyes of patients with cytomegalovirus retinitis and according to CD4+ T cell count at enrollment

	Visual Field Outcomes			
Rate/Eye-year (95% Confidence interval)	< 700 degrees [*]	< 600 degrees (75% of normal) [†]	< 400 degrees (50% of normal)	< 80 degrees (10% of normal)
Overall Rate	0.35	0.22	0.08	0.01
	(0.32, 0.39)	(0.20, 0.25)	(0.06, 0.10)	(0.008, 0.02)
Baseline CD4+ T cell count				
< 50 cells/μL	0.57	0.38	0.14	0.02
	(0.49, 0.65)	(0.32, 0.45)	(0.11, 0.17)	(0.01, 0.04)
50-100 cells/μL	0.39	0.27	0.09	0.01
	(0.32, 0.55)	(0.15, 0.30)	(0.06, 0.12)	(0.004, 0.03)
101-199 cells/μL	0.35	0.28	0.08	0.01
	(0.27, 0.48)	(0.21, 0.37)	(0.05, 0.10)	(0.004, 0.02)
≥ 200 cells/μL	0.22	0.14	0.06	0.008
	(0.19, 0.25)	(0.11, 0.17)	(0.05, 0.07)	(0.004, 0.01)

* Visual field score that represents 2 standard deviations from the median visual field score among individuals without ocular disease (see Reference 21).

[†] Represents percent of normal visual field score.

Table 3

Rates of loss of visual field among eyes affected with cytomegalovirus retinitis

Risk factor	Visual field loss to < 60° (75% of normal field)			Visual field loss to < 40° (50% of normal field)		
	n/N	Rate/EY	P-value	n/N	Rate/EY	P-value
Age at enrollment < 41 years ≥ 41 years	43/118 41/110	0.24 0.19	0.21	64/218 92/232	0.08 0.08	0.59
Gender Female Male	17/46 69/157	0.21 0.20	0.96	33/87 102/339	0.12 0.10	0.35
Race Nonwhite White	46/91 38/92	0.25 0.18	0.21	84/233 72/214	0.10 0.07	0.17
HIV risk factor MSM only Injection drug use Heterosexual	53/115 9/17 19/44	0.20 0.24 0.19	0.66	45/205 3/10 19/71	0.07 0.09 0.10	0.53
CD4+ T-cell count* 0-49 cells/μL 50-100 cells/μL 101-199 cells/μL ≥ 200 cells/μL	71/170 9/59 15/85 41/118	0.43 0.28 0.26 0.18	<0.001	38/100 16/52 13/76 51/117	0.17 0.08 0.07 0.06	0.001
HIV viral load in log ₁₀ (copies/mL)* < 2.60 2.60 – 4.00 4.00 – 5.00 > 5.00	53/115 61/127 45/91 52/110	0.15 0.21 0.25 0.39	<0.001	43/221 46/241 28/162 33/164	0.05 0.08 0.10 0.15	<0.001
HAART* No Yes	12/50 75/171	0.31 0.18	0.001	26/142 107/340	0.12 0.08	0.008
Immune recovery*† No Yes	52/122 84/178	0.41 0.17	<0.001	62/220 74/245	0.14 0.06	<0.001
IRU* No Yes	79/177 5/19	0.21 0.23	0.95	117/368 13/58	0.08 0.09	0.46
Anti-CMV therapy* GCV implant Intravitreal injection Systemic GCV	8/395/9 5/23 41/134 62/88	0.18 5.03 0.37 0.15 0.29	0.002	32/94 3/8 21/69 42/114 20/83	0.09 2.51 0.14 0.06 0.12	<0.001

Risk factor	Visual field loss to < 600° (75% of normal field)			Visual field loss to < 400° (50% of normal field)		
	n/N	Rate/EY	P-value	n/N	Rate/EY	P-value
None with immune recovery None without immune recovery						
Active CMVR at enrollment	106/164	0.19	<0.001	108/374	0.08	
No	19/67	0.76		20/107	0.36	<0.001
Yes						

CMV = cytomegalovirus; CMVR = cytomegalovirus retinitis; EY = eye-year; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; IRU = immune recovery uveitis; MSM = men having sex with men.

*Time updated analyses at visit before the event. NOTE = analyzing CMV therapy at baseline only yielded similar results.

†Immune recovery defined as CD4+ T cell count > 100 cells/ μ L.

Table 4

Final multiple regression model of risk factors for loss of visual field among eyes affected with cytomegalovirus retinitis

<i>Risk Factor</i>	<i>Visual field loss to < 600* (75% of normal field)</i>		<i>Visual field loss to < 400* (50% of normal field)</i>	
	Crude RR (95% CI, P)	Adjusted RR* (95% CI, P)	Crude RR (95% CI, P)	Adjusted RR* (95% CI, P)
CD4+ T-cell count [†]				
0-49 cells/μL	2.70 (1.93, 3.78, <0.001)	2.01 (1.42, 2.85, <0.001)	3.00 (2.20, 4.00, <0.001)	2.12 (1.30, 3.46, 0.003)
50-100 cells/μL	2.33 (1.45, 3.74, <0.001)	1.80 (1.19, 2.74, 0.006)	2.30 (1.50, 3.53, <0.001)	2.07 (1.28, 3.35, 0.003)
101-199 cells/μL	1.91 (1.37, 2.67, <0.001)	1.67 (1.12, 2.51, 0.01)	1.34 (0.88, 2.03, 0.17)	1.38 (0.88, 2.16, 0.16)
≥ 200 cells/μL	1.00 (reference)	1.00 (reference)	1.00	1.00 (reference)
HIV viral load [†]				
<2.60 log ₁₀ (copies/mL)	1.00 (reference)		1.00 (reference)	
2.60-4.00 log ₁₀ (copies/mL)	1.59 (1.14, 2.21, 0.006)		1.70 (1.21, 2.40, 0.002)	
4.00-5.00 log ₁₀ (copies/mL)	1.60 (1.19, 2.19, 0.002)		1.98 (1.33, 2.95, 0.001)	
> 5.00 log ₁₀ (copies/mL)	2.43 (1.77, 3.34, <0.001)		2.83 (1.93, 4.14, <0.001)	
HAART use [†] (yes vs no)				
	0.58 (0.41, 0.82, 0.002)	0.72 (0.54, 0.95, 0.02)	0.73 (0.46, 1.16, 0.18)	0.80 (0.56, 1.14, 0.22)
Immune recovery ^{†‡} (yes vs no)				
	0.46 (0.37, 0.58, <0.001)		0.41 (0.29, 0.58, <0.001)	
Zone 1 retinitis [†]				
	1.83 (1.39, 2.41, 0.001)		3.31 (2.33, 4.70, <0.001)	
Retinal area >25% [†]				
	2.41 (1.80, 3.22, <0.001)	1.51 (1.16, 1.97, 0.002)	6.52 (4.38, 9.71, 0.001)	3.82 (2.75, 5.30, <0.001)
Active retinitis [†]				
	4.73 (3.24, 6.91, <0.001)	3.31 (2.36, 4.63, <0.001)	5.72 (2.16, 6.39, 0.004)	2.70 (1.74, 4.21, <0.001)

HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; RR = relative risk; 95% CI = 95% confidence interval.

* Analyses controlled for baseline demographic characteristics. The variable immune recovery was dropped from these analyses due to a high level of correlation with CD4+ T cell count (> 0.90).

[†]Time updated analyses

[‡]Immune recovery is defined as a CD4+ T cell count < 100 cells/μL.

Table 5

Rates of visual field loss in patients with cytomegalovirus retinitis prior to and during the era of highly active antiretroviral therapy

	Rate of visual field loss to 50% loss among affected eyes [*]	Rate of visual field loss to 90% loss among affected eyes [*]
Pre-HAART era		
FGCRT	0.59	0.20
CRRT	0.53	0.23
HAART era		
LSOCA overall	0.08	0.02
LSOCA with active retinitis and without HAART	0.34	0.06
LSOCA with active retinitis	0.26	0.05
LSOCA without IR	0.11	0.02
LSOCA with IR	0.04	0.008
LSOCA with IRU	0.05	0.01
LSOCA without IRU	0.04	0.008

HAART = highly active antiretroviral therapy, FGCRT = Foscarnet-Ganciclovir CMV Retinitis Trial, CRRT = CMV Retinitis Retreatment Trial, LSOCA = Longitudinal Study of Ocular Complications of AIDS, IR = immune recovery, IRU = immune recovery uveitis.

* 50% loss = 350 degrees of visual field loss; 90% loss = 630 degrees of visual field loss. Based on a normal visual field score of 700 degrees—the definition used in the pre-HAART studies (From: Studies of Ocular Complications of AIDS (SOCA) Research Group in collaboration with the AIDS Clinical Trials Group (ACTG). Studies of Ocular Complications of AIDS Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 1. Rationale, design, and methods. Control Clin Trials 1992;13:22-39.).